

Original
article

Heterosexual HIV transmission and STD prevalence: predictions of a theoretical model

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Background: Previous studies suggest that concurrent sexually transmitted infection may enhance HIV transmission. This paper explores some theoretical consequences of this using a mathematical model of transmission of HIV and other STD pathogens.

Objectives: To develop a deterministic mathematical model to describe the heterosexual transmission dynamics of both HIV and a bacterial STD.

Study design: We used survey derived estimates of sexual behaviour in a young heterosexual London population in our deterministic mathematical model to estimate the effects on an HIV epidemic of different levels of STD prevalence in such a population.

Results: We show that the predictions of the model are plausible and suggest that, even under conditions both of low STD prevalence and of low HIV transmission enhancement, a substantial proportion of HIV transmission events may be attributable to concurrent STD.

Conclusions: It is likely that epidemics of heterosexually transmitted HIV infection in industrialised countries have been limited in size by the relative success of efforts to control STD. None the less, a significant proportion of heterosexual transmission events which do occur may be attributable to concurrent STD. In developing countries, cheap and simple STD care is likely to be a highly cost effective strategy to prevent HIV transmission.

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Keywords: HIV transmission; STD prevalence; model

Introduction

Marked differences in the size of the epidemics of human immunodeficiency virus (HIV) infection in different parts of the world are well recognised but poorly understood. In particular, HIV prevalence among heterosexuals has increased more rapidly, and reached higher levels in many developing countries compared with industrialised countries. During the 1980s explanations for this were generally couched in terms of differences either in patterns of sexual behaviour or in the potential for medically related transmission. In 1988 it was proposed that the higher HIV prevalence found in some developing countries might be explained by the concomitantly higher prevalence of sexually transmitted diseases (STD), if the presence of STD in an HIV exposed or infected individual enhanced the transmission of HIV.¹ There are several mechanisms through which such enhancement might be effected. An STD which leads to ulceration of the genital skin or mucosa might facilitate ingress or egress of HIV carrying body fluids.^{1–3} Some of the inflammatory cells which infiltrate and shed from genital mucosa in the presence of various STDs are known to be primary targets for HIV infection,^{4,5} and the presence of inflammatory cells in the male and female genital tract has been shown to be correlated with the presence and quantity of HIV detectable in sperm,^{6,7} and cervicovaginal secretions.⁸

It has been more difficult to obtain direct epidemiological evidence to support the transmission enhancement hypothesis. Observational studies have reported increased relative risks of HIV acquisition among people with

STD infections,^{9,10} but have been criticised for failing to achieve adequate control of confounding due to sexual behavioural factors. Difficulty in achieving adequate control of confounding led some to suggest that the transmission enhancement hypothesis could only adequately be tested through randomised studies of interventions to reduce STD prevalence.^{11,12} The first such intervention study to be reported¹³ did demonstrate a substantial effect in reducing HIV incidence, and has led to a call for the rapid development of STD treatment programmes in developing countries as a primary component of HIV control.¹⁴

Estimates of the proportion of sexually transmitted HIV infections attributable to the presence of STD in populations with different levels of STD prevalence are needed to assess both the feasibility of controlling HIV transmission through enhancing STD control, and the relative efficiency of this approach relative to other HIV preventive interventions. Individuals who have, or are at increased risk of, HIV infection because they have less safe sexual behaviour are, for the same reason, more likely to have STDs. Therefore the relation between the enhancement of HIV transmission at the individual level and the proportion of prevalent HIV cases attributable to STD in a population is likely to be non-linear, except in the early stages of the epidemic. Mathematical techniques which model the transmission of STD and HIV within a population together with transmission enhancement effects represent an obvious approach to describing the effects of this non-linearity.

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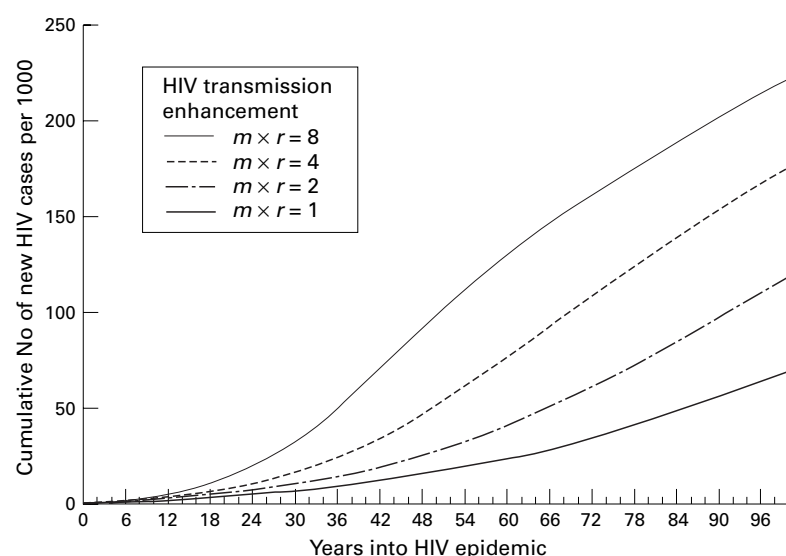


Figure 1 Cumulative HIV infections over time for different levels of transmission enhancement (STD prevalence 1.5%).

May and Anderson have considered the case where an STD exists concomitantly with HIV in a population.¹⁵ They show that in the absence of enhanced transmission a high degree of association between HIV infection and STD can be expected to arise purely from confounding with numbers of sexual partnerships. They also show that where there is enhanced transmission, then in the early stages of an HIV epidemic, the effect of an STD which enhances HIV transmission by a factor a if either partner has the STD and a^2 if both do, is to increase the basic reproductive rate R_0 of the HIV epidemic by a factor a^2 times the STD prevalence. The effective rate of partner change (the rate at which a behaviourally homogeneous population would sustain the same prevalence of a disease as seen in a heterogeneous population) is shown to be increased from $\langle i^2 \rangle / \langle i \rangle^2$ towards $\langle i^3 \rangle / \langle i^2 \rangle$ where i is the partner change rate in a stratum and the angle brackets denote arithmetic mean for the whole population.

Robinson and colleagues¹⁶ have reported the findings of a microsimulation using parameters of sexual behaviour measured in a rural Ugandan population. They used HIV transmission probabilities of one in 1000 per sex act in mid infection, and 1 in 100 in the early and late stages of pre-AIDS HIV infection, and applied local estimates of the prevalence of ulcerative and non-ulcerative STD. Predicted proportions of prevalent sexually transmitted HIV infections attributable to concurrent STD range from 93% to 99% in the first 10 years of the HIV epidemic, and between 38% to 83% in next 10 years, depending on the level of enhancement.

Overview of methods

In this paper we use a deterministic mathematical model to describe the heterosexual transmission dynamics of both HIV and a bacterial STD. We build on the standard compartmentalised model for a closed population, of the sexual transmission of infections developed by Hethcote and York,¹⁷ Anderson,¹⁸ and others

by introducing terms describing increased HIV transmission in the presence of an STD. We use the model to explore the effects of achieving different levels of STD control in a population with sexual behaviour which is similar to that of heterosexual men and women in London.

Details of the model and parameter estimates we use are given in the appendix. We have chosen values for the STD transmission probabilities per partnership and average durations of infection which give plausible STD prevalences consistent with levels of control achieved in a variety of industrialised countries. We use estimates of the transmission probability of HIV consistent with published estimates. In order to simplify the modelling we assume that the enhancement of HIV transmission probability within a partnership is the same whether the HIV infected (enhancement factor = m) or the HIV uninfected individual has the STD (enhancement factor = r); that is $m = r$. In addition, if both are infected we assume that the HIV transmission probability is increased by a factor $m \times r$. Both these assumptions were used in previous work by May and Anderson.¹⁵ We model the effects of various levels of enhancement, with the product $m \times r$ taking values of 1 (no STD enhanced HIV transmission) 2, 4, and 8. Estimates of the distribution of the population across sexual contact rate strata are derived from the United Kingdom National Survey of Sexual Attitudes and Lifestyles (NSSL).¹⁹ We assume proportional mixing between these strata which we have previously shown is reasonable for this population.²⁰

We used standard numerical methods to calculate the prevalences of STD and HIV in each age/sex stratum over time. We first allowed the STD prevalence to achieve its non-zero endemic equilibrium within the population. We then introduced HIV into the population at a prevalence of 0.1% and calculated the predicted evolution of HIV and STD occurrence over time. Year zero in the results presented below designates the point of introduction of HIV. We ran different models for the different chosen STD equilibrium prevalences and for the different levels of HIV transmission enhancement: $m \times r$.

Results

Figure 1 shows the predicted evolution of the cumulative number of new HIV infections per 1000 initial population for levels of HIV transmission enhancement: $m \times r = 1$ (no STD enhanced HIV transmission), 2, 4, and 8; and for an equilibrium STD prevalence of 1.5% (which may be a realistic level for an infection such as *Chlamydia trachomatis* in a young heterosexual London population).^{21–23} As expected, the higher levels of transmission enhancement produce higher cumulative numbers of new infections. For $m \times r = 2$ the cumulative number of new HIV infections occurring by 16 years was 1.25 fold greater than in the absence of transmission enhancement. For $m \times r = 4$ and $m \times r = 8$ the corresponding ratios are 1.70 and 2.71 respectively.

Figure 2 shows the predicted evolution of the prevalence of HIV infection in the population for a fixed level of transmission enhancement: $m \times r = 2$. In other words we make the very modest assumption that if one partner has the STD, the probability of HIV transmission is increased by a factor of 1.41. The individual curves show the HIV prevalences predicted for the different levels of STD prevalence: 1.5%, 4%, 10%, and 22%.

With a low STD prevalence (1.5%) such as might be encountered for *Chlamydia trachomatis* in a industrialised country²¹⁻²³ the HIV prevalence increases 2.4-fold over the first 16 years compared with a 1.9-fold increase in the absence of STD. For the higher STD prevalences the corresponding increases over 16 years were 3.5-fold for an STD prevalence of 4%, 7-fold for an STD prevalence of 10%, and 10-fold for an STD prevalence of 20%. For 20% STD prevalence this represents an HIV prevalence of 1% at 16 years, subsequently rising to a maximum of 5.4% at 48 years.

We have carried out identical analyses for higher levels of HIV transmission enhancement corresponding to $m \times r = 4$ and $m \times r = 8$. The overall forms of the curves obtained (not shown) are very similar to those shown in figure 2. The effect of increasing transmission enhancement is to stretch the curves vertically and to compress them horizontally. For example, for $m \times r = 4$ the HIV prevalence increases 3.3-fold over 16 years with STD prevalence = 1.5%, 9.2-fold with STD prevalence = 4%, 40-fold with STD prevalence = 10%, and 70-fold with STD prevalence = 20%; representing, in the latter case, an HIV prevalence of 7%, subsequently rising to a maximum of 8.7% at 28 years.

For $m \times r = 8$ the HIV prevalence increased 5.4-fold over 16 years with STD prevalence = 1.5%, 34-fold with STD prevalence = 4%, 93-fold with STD prevalence = 10%, and 120-fold with STD prevalence = 20%, representing in the latter case, an HIV prevalence of 12%, subsequently rising to a maximum of 12.2% at 20 years.

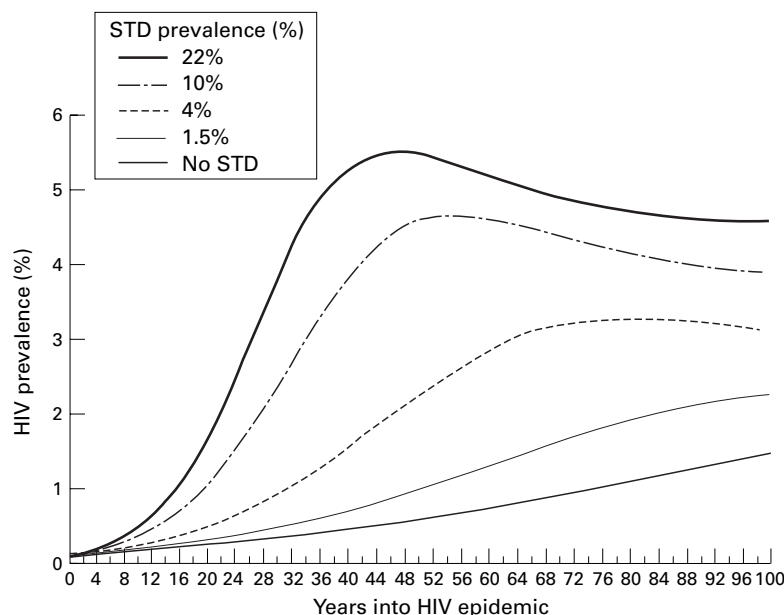


Figure 2 HIV prevalence over time for different STD prevalences ($m \times r = 2$).

Discussion

Our findings represent an initial attempt to use a deterministic mathematical model to describe the heterosexual transmission of HIV and a single STD, and the enhancement of transmission of HIV by that STD, in an urban setting in a industrialised country, utilising empirically derived measures of sexual behaviour. Building on previous work with single infection STD models, we have accomplished this. However, there are a number of simplifying assumptions inherent in the structure of the model as well as uncertainties over the accuracy of the estimates we use for some of the parameters.

The model does not distinguish between concurrent and monogamous sexual partnerships and there are reasons to believe that concurrence may be an important determinant of transmission dynamic.^{24, 25} In contrast with Robinson and colleagues¹⁶ our approach has modelled transmission upon risk per partnership, and therefore neither incorporates distinctions between short and long partnerships, nor models the number of sex acts within a partnership. However, previous work suggests that the number of sex acts which take place within a partnership is not an important determinant of transmission.²⁶

We have not modelled possible variability in the transmission probability of HIV from an infected individual during the course of the infection either as a result of antiviral therapy or natural history. Neither have we modelled the effects of possible heterogeneity in either host susceptibility to infections or in pathogen strain infectivity. However, our model could potentially be further developed to account for heterogeneity and variation in such factors when further information describing these becomes available. We have used a purely heterosexual transmission model which does not account for the repeated introduction of HIV infection into the population through contacts with injecting drug users or bisexuals.

We have used a transmission probability for HIV of 0.01 per partnership in the absence of STD, which is slightly below the lowest estimate reported by Anderson and May,²⁷ (range 0.03–0.18 for male to female HIV transmission from haemophilic and transfusion related cases in stable relationships) and which ignores any effect resulting from individuals with STDs practising safer sex as a consequence. In our model, the effect of increasing the HIV transmission probability from 0.01 to 0.1 (roughly the midpoint of the estimates by Anderson and May²⁷), using the London heterosexual partnership rates, was to produce totally unrealistic HIV prevalence (25% HIV prevalence 16 years into the epidemic in the absence of STD). More recent and reliable studies²⁸⁻³⁰ estimate transmission probability to be closer to 0.05 in partners of known HIV infected individuals. However these studies also show considerable enhancement of HIV transmission where HIV disease was more advanced. Such studies necessarily only observe subjects who are known to be HIV positive. Therefore, the proportion of cases in

these studies who were at the more advanced stage of HIV disease is likely to be considerably greater than among all heterosexuals with HIV infection (diagnosed and not-diagnosed) in London. It therefore seems reasonable to assume an average transmission probability considerably below 0.05, but we cannot be certain of this.

Despite these assumptions and uncertainties, the model predicts a plausible pattern of evolution of HIV infection over time in the population of London heterosexuals. Data from the UK unlinked anonymous HIV seroprevalence study show HIV prevalence in representative samples of pregnant women in London to have increased from 0.18% in 1990 to 0.31% in 1995.³¹ In comparison, our model predicts that with $m \times r = 2$ this increase would require 18 years in the absence of STD, 12 years with STD prevalence = 1.5%, 7 years with STD prevalence = 4%, 5 years with an STD prevalence of 10%, and 4 years with STD prevalence of 22%. The predicted period of time to achieve this is of course shorter with higher levels of HIV transmission enhancement.

We do not have accurate empirical estimates of the real levels of any enhancement which may be engendered by different STDs. However, our model predicts that even at low levels of enhancement and STD prevalence, significant proportions of heterosexually acquired HIV infections will be attributable to STD. When higher but still relatively modest levels of enhancement are modelled (cf Robinson *et al*¹⁶) the proportion of cases attributable to STD becomes a majority. If the prevalence of STD within a population increases from the levels observed in urban heterosexual populations in industrialised countries for chlamydial infection^{21–23} to those in developing countries,³² then a pattern of evolution of HIV prevalence commensurate with that observed in developing countries is predicted. This suggests that the patterns of the epidemics in developing countries may result from poor STD control rather than significant differences in sexual behaviour. Grosskurth and colleagues¹³ have already shown that cheap and simple STD care is likely to be a highly cost effective strategy to prevent HIV transmission in these countries.

It is likely that epidemics of heterosexually transmitted HIV infection in industrialised countries have been limited in size by the relative success of efforts to control STD. None the less, a significant proportion of heterosexual transmission events which do occur may be attributable to concurrent STD. Our findings highlight the importance of continuing to promote STD control as a major element of HIV prevention globally.

Appendix: The mathematical model

We consider a population with sex denoted by the subscripts k and k' , and having a number of discrete sexual contact rate strata represented algebraically either by the subscripts i or j . The subscripts h and s used in some of the terms denote that the term relates respectively to HIV infection or to STD (for example, gonorrhoea)

infection. The basic differential equation giving the number of HIV infected individuals (infected) in a population is given in equation (1).^{17 18}

$$\frac{dY_{hki}}{dt} = \beta_{hk} \theta_{ki} c_{ki} X_{hki} \sum_j p_{kji} \phi'_{kj} \left[\frac{Y_{hki}}{N_{ki}} \right] - v_h Y_{hki} \quad (1)$$

The principal terms have the following meanings:

N_{ki} : population size (for sex k , activity stratum i).

Y_{hki} : number of HIV infected in N_{ki} .

X_{hki} : number of HIV susceptibles in N_{ki} , ($= N - Y$).

β_{hk} : probability of HIV transmission to a susceptible of sex k from an HIV infected of opposite sex, per partnership (in the absence of STD). sexual contact rate for sex k , stratum i —that is, the number of new sexual partners per unit time.

c_{ki} : sexual contact rate for sex k , stratum i —that is, the number of new sexual partners per unit time.

v_h : removal rate from the sexually active population of those with HIV infection (all causes including AIDS morbidity and mortality).

p_{kij} : an element of the sexual mixing matrix—that is, the proportion of partners of those of sex k , stratum i , who come from stratum j of the opposite sex.

With the exception of the terms θ and ϕ , this is the standard model, using the notation of Garnett and Anderson.³³ θ and ϕ are both functions of STD prevalence, and represent the enhanced HIV transmission probabilities due to concurrent STD in the HIV susceptibles and infected respectively. We assume that the HIV transmission probability β_{hk} is multiplied by a factor m if an HIV susceptible individual has an STD infection, and by a factor r if an HIV infected individual has an STD infection. Then for an HIV susceptible person of sex k , stratum i having sex with an HIV infected person of sex k' and stratum j , the transmission probability β_{hk} is multiplied by the factor θ_{ki} to account for STD prevalence in the susceptible's stratum, and by a factor ϕ_{kj} to account for STD prevalence in the infected persons

$$\theta_{ki} = f \left[\frac{Y_{ski}}{N_{ki}} \right] = 1 + (m - 1) \frac{Y_{ski}}{N_{ki}} \quad (2)$$

stratum, where

$$\phi_{kj} = f \left[\frac{Y_{skj}}{N_{kj}} \right] = 1 + (r - 1) \frac{Y_{skj}}{N_{kj}} \quad (3)$$

and Y/N represents STD prevalence. There is an implicit assumption that the presence of STD has no effect on partner acquisition or partner choice.

The STD prevalence, which must be determined in order to establish θ and ϕ is obtained with the standard equation for a compartmentalised model. The STD model is:

$$\frac{dY_{ski}}{dt} = \beta_{sk} c_{ki} X_{ki} \sum_j p_{kij} \left[\frac{Y_{skj}}{N_{kj}} \right] - v_s Y_{ski} \quad (4)$$

It should be noticed that equation (4) implies that at equilibrium it is only the ratio β_s/v_s , rather than the particular values of β_s or v_s , which determines the prevalence within each stratum. We also introduce an expression for changes in the size of strata over time which takes into account HIV related mortality and morbidity:

$$\frac{dN_{ki}}{dt} = R_{ki} - \frac{(N_{ki} - Y_{hki})}{d} - \frac{Y_{hki}}{f} \quad (5)$$

where R_{ki} is a constant inflow (that is, the number of people per unit time recruited into the sexually active population), d is the average duration for which individuals without HIV are sexually active, and f is the duration for which those with HIV remain sexually active, accounting for the extra mortality and morbidity caused by HIV.⁸

VALUES FOR PARAMETERS AND VARIABLES

We use a range of estimated values for β_s/v_s for a notional STD. These are chosen to generate equilibrium prevalences (1.5%, 4%, 10%, 22%) consistent with levels of control of bacterial STD achieved in a variety of industrialised and developing countries.³² These are consistent reported empirical estimates.³⁴ Values of $\beta_{s(\text{male})}/v_s$ and $\beta_{s(\text{female})}/v_s$ used to generate the above equilibrium prevalences were respectively: $\beta_{s(\text{male})}/v_s = 0.9, 1.2, 2.4, 6.0$ months and $\beta_{s(\text{female})}/v_s = 1.2, 1.6, 3.2, 8.0$.

Table A1 Estimates of parameters and variables used in the model including STD transmission parameters for four different scenarios labelled (a)–(d)

Parameter/variable	Estimate/value			
Transmission parameters for STD:				
	(a)	(b)	(c)	(d)
$\beta_{s(Male)}/v_i$	0.9	1.2	2.4	6 months
$\beta_{s(female)}/v_i$	1.2	1.6	3.2	8
Transmission parameters for HIV:				
$\beta_{h(Male)}$	0.01			
$\beta_{h(female)}$	0.01			
v_h	0.1			per year
Population description by stratum:				
$N_{male} 0$	152			
$N_{male} 1$	278			
$N_{male} 2$	87			
$N_{male} 3$	41			
$N_{female} 0$	62			
$N_{female} 1$	447			
$N_{female} 2$	49			
$c_{male} 0$	0			partners/year
$c_{male} 1$	0.52			
$c_{male} 2$	2.24			
$c_{male} 3$	18.1			
$c_{female} 0$	0			partners/year
$c_{female} 1$	0.52			
$c_{female} 2$	17.3			

We use an estimate of the HIV transmission probability per partnership (β_h) of 0.01 in either direction. There is considerable uncertainty as to the true average value for this parameter for our population. The value we chose is below the lower bound of the range suggested by Anderson and May²⁷ in 1988, but is, we believe, more consistent with recent and better estimates,^{28–30} and was chosen to generate plausible estimates of heterosexually acquired HIV infection in the London population. Our estimate of the average period for which an HIV uninfected person remains sexually active, d , is 30 years, and for an HIV infected person, f , is 10 years.

The distribution of the population across sexual contact rate strata is derived from the London sample of the NSSAL¹⁹ aged between 16 and 35 years who had not had a same sex partner within the past 5 years. We use instantaneous contact rates calculated from detailed information obtained through NSSAL, describing the timing of initiation of new partnerships. Cut off points defining ranges of individual contact rates are chosen to generate four strata for males and three for females, and within stratum average contact rates were used as estimates of c_{ki} for each stratum. The strata chosen represent a compromise between achieving the contribution of roughly equal numbers of partnerships by each stratum and having sufficiently large numbers of individuals in the highest contact rate strata in the NSSAL sample to avoid excessive sampling error. We have addressed the problem of the higher total number of partnerships reported by men than by women in the NSSAL sample^{34–36} by adjusting the contact rate of the highest activity female stratum to make these numbers consistent. Parameter values used were as follows: $c_{\text{male } 0} = 0$, $c_{\text{male } 1} = 0.52$, $c_{\text{male } 2} = 2.24$, $c_{\text{male } 3} = 18.1$, $c_{\text{female } 0} = 0$, $c_{\text{female } 1} = 0.52$, $c_{\text{female } 2} = 17.3$ (partners per year). In the model HIV related mortality produces an imbalance between sex and activity strata with respect to the total number of female partners “required” by males compared with the total number of male partners “required” by females. The number of partners in the male activity strata is therefore multiplied by a factor that varies with time, calculated to keep the total number of partnerships consistent between sexes. The estimates used were

$$N_{\text{male } 0} = 152, N_{\text{male } 1} = 278, N_{\text{male } 2} = 87, N_{\text{male } 3} = 41, N_{\text{female } 0} = 62, N_{\text{female } 1} = 447, N_{\text{female } 2} = 49$$

In order to simplify the modelling we assume that the enhancement of HIV transmission probability within a partnership is the same whether the HIV infected or the HIV uninfected individual has the STD—that is, $m = r$. In addition if they are both infected we assume that the HIV transmission probability is increased by a factor $m \times r$. Both these assumptions were also used in previous work by May and Anderson.¹⁵ We model the effects of various levels of enhancement, with the product $m \times r$ taking values of 1 (no STD enhanced HIV transmission) 2, 4, and 8.

RUNNING THE MODEL

We used a first order Runge–Kutta numerical method to calculate the form of V_{ski} , V_{hki} and N_i in equations (1), (4), and (5) as a function of time, using a step size of 0.1 months. We first allowed the STD prevalence to achieve its non-zero endemic equilibrium within the population. We then introduced HIV into the population at a prevalence of 0.1% and calculated the predicted evolution of HIV and STD occurrence over time. Year zero in the results presented in table A1 designates the point of introduction of HIV. We ran different models for the different chosen values of β_s/v_s (that is, the STD transmission parameters) shown under columns (a) to (d) in table A1, and for the different values $m \times r$ described in the previous paragraph.

Contributors: The idea of developing a combined model of HIV/STD transmission in the London heterosexual population was conceived by Dr Renton. The development of the model came from discussions among all three authors. The development of the algebraic form of the equations was carried out by Luke Whitaker, in discussion with Adrian Renton and Mark Riddlesdell. The computer programming and production of the numerical outputs was carried out by Mark Riddlesdell, under the supervision of AR and LW. The first draft of the paper was prepared by AR and subsequent revisions were carried out by AR.

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